CHIRON

July 27, 2004

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, Maryland 20852

Re: Critical Path Initiative [Docket No. 2004-N-0181, 69 *Federal Register*, 21839 (April 22, 2004)]

Dear Madam/Sir:

On behalf of Chiron Corporation please find attached our thoughts for your consideration as you craft a critical path opportunities list outlining areas of product development that could most benefit from innovative approaches and technological advances. We have focused our recommendations on the area of oncology, a pressing and high priority area of research. We believe that key steps taken by the Food and Drug Administration in collaboration with the private sector and academia will serve to accelerate oncology products from preclinical development to the market. We look forward to continued collaboration and communication with you as the agency identifies the key priority areas this fall.

Please do not hesitate to contact us directly for additional information or clarification of any of the enclosed recommendations.

With best regards.

Sincerely,

Marguerite Baxter

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2004N-0181

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Regulatory Approaches to Improving Oncology Clinical Trials

A limited number of key regulatory changes could significantly improve the effectiveness of and reduce the resources required to conduct clinical trials in oncology:

- Improved regulatory pathways for registering the *combination* of a test or marker together with a cancer drug;
- Regulatory approaches that allow for testing of new therapies in earlier stages of disease, with enhanced post-marketing surveillance to ensure those therapeutics deliver on their promise;
- Guidelines promoting trials in healthier patient populations that are better able to support efforts to advance scientific understanding of cancer; and
- A national trial enrollment infrastructure, with active internet-based patient recruitment.

Issue 1: Cancer trials have unusually high failure rates. Oncology drug development programs progress from Phase II to the market only 10% of the time, less than half the success rate seen in for other human diseases.

- A key cause is the historic tendency to recruit patients based on cancer type (e.g., breast, lung, or colon), rather than a cancer mechanism.
- A second cause has been the evaluation of a treatment's early success by anatomical characteristics (e.g., tumor shrinkage), rather than functional characteristics (e.g., reduction in cancer metabolism).
- Both tendencies are rooted in an era where the key underlying mechanisms behind neoplastic transformation were poorly understood, and in which there was no way to directly probe the functionality of tissue rather than its mere presence.
- However, the last decade has seen a radical improvement in our understanding of key mechanisms behind the development of cancer, as well as the availability of improved diagnostic technologies (e.g., PET imaging has allowed us to evaluate the functional properties of living tissue deep within the body).

Action: Better define the regulatory pathways for targeted therapies, particularly those that rely on diagnosis of disease mechanism and monitoring of functional tumor biology.

- It remains difficult to register the combination of a targeting drug and the clinical test that identifies patients who will most benefit from treatment with it.
- Clinical endpoints that were acceptable in the absence of technology to identify functional changes in tumor biology have not been updated to reflect our new capabilities.

Issue 2: Current treatment guidelines compel newer cancer drugs to be tested in sub-optimal patient populations.

- Many newer targeted therapies are more likely to work earlier in the disease process, and/or in combination with other unapproved drugs.
- Most of the small percentage of cancer patients who participate in clinical trials for new drugs have progressed to the point where their disease is less susceptible to newer targeted therapies.
- Most new cancer therapies are tested only on patients in whom all other therapies have failed, and those whose cancers have become the most resistant to treatment.

Action: Regulatory approaches that use surrogate or non-mortality endpoints and biomarkers (with greater post-marketing surveillance) to promote early intervention in disease progression.

- New technologies that facilitate earlier demonstration of a drug's biological activity allow for trial designs that rely on endpoints other than mortality or progression of disease.
- Identification of biomarkers that predict the success of new cancer medicines would speed new drug development and reduce reliance on conventional and time-consuming endpoints such as survival time.
- Clear agency guidelines on the status of and requirements for biomarker usage will speed the development of new therapeutics.

Issue 3: Cancer trials are often scientifically unproductive

- As mentioned earlier, most cancer patients receive an approved therapy - which in many cases is insufficient for cure – until their disease has progressed to the point that existing therapies no longer work.
- By the time they enter clinical trials, many of these patients are fragile and do not tolerate the disruption of care and the sampling of tissue which are critical to obtaining tumor cells for scientific analysis.
- As a result, less is known about many scientific questions in cancer, such as the interaction of tumors with the surrounding tissues, than might otherwise be the case.

Action: Regulatory approaches that promote the testing of therapies in earlier stage disease (and healthier patient populations) would facilitate a greater scientific understanding of cancer.

- Use of biomarkers to guide diagnosis and treatment would help the patient better tolerate necessary scientific and clinical testing required to improve our understanding of cancer.

Issue 4: Cancer trials are too lengthy

- Arduous clinical endpoints and low patient enrollment rates lead to very long pivotal trials.
- According to a 1999 study conducted by ASCO, while 20% of them meet eligibility requirements, only 3% of adult cancer patients sign up for clinical trials.
- Cancer trials are dramatically more expensive than those in many other therapeutic areas, and means that needed medications become available much more slowly.

Action: Create a comprehensive, national, internet-based clinical trial recruitment and enrollment infrastructure with support from industry and government entities.

- A secure, distributed database with relevant clinical and biological information and patient privacy protection is needed for all US cancer patients.
- Sponsoring institutions could work through qualified third parties to rapidly identify a prospective patient pool of the correct patients for an experimental therapy.
- A number of current regulations would require updating in order to permit this approach, but its impact on patient recruitment, duration of trials, and the availability of effective medications would be substantial.

Conclusion

A limited number of regulatory changes could result in a dramatic improvement in the efficiency and effectiveness of clinical cancer research – and therefore dramatic progress in our ability to fight this disease.

Updating an outdated paradigm to accommodate development of targeted cancer therapeutics would require

- Enhancing our ability to co-commercialize both a drug and a test;
- Alternative, biology-based trial endpoints to get patients enrolled earlier and in a more healthy condition;
- Permitting drugs to be marketed sooner, while improving our post-marketing surveillance in case a marketed drug fails to live up to its earlier promise; and
- Initiating a comprehensive plan to create and support an active national trial recruitment infrastructure.

These are difficult tasks, but each of them can be accomplished. The reward for doing so, in terms of our ability to offer hope to patients and our ability to deliver on that promise, could be tremendous.